Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve

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Aims To investigate the relationship between adrenal gland function and pressor response to noradrenaline in septic shock.

Methods Basal cortisol level, noradrenaline—mean arterial pressure dose-response curve and cortisol response to intravenous corticotrophin bolus were obtained in nine patients fulfilling usual criteria for septic shock and in six normal volunteers. In patients with septic shock, dose-response curve to noradrenaline was determined a second time 60 min after a 50 mg intravenous hydrocortisone bolus.

Results As compared with controls, patients with septic shock had increased basal cortisol levels (mean $\pm$ s.d.: 1564 ± 818 *vs* 378 ± 104 nmol l^{-1}, $P=0.002$, 95% confidence interval for difference in means: [452, 1920]) and a blunted cortisol response to corticotrophin (403 ± 461 *vs* 1132 ± 195 nmol l^{-1}, $P=0.008$, [-1163, -295]). Five patients had impaired adrenal function reserve. As compared with controls, septic patients displayed a moderate and non significant decrease in pressor sensitivity to noradrenaline ($P=0.112$). As compared with patients with adequate adrenal response, patients with impaired adrenal function reserve showed a significant decrease in pressor sensitivity to noradrenaline ($P=0.038$). In septic patients, hydrocortisone improved pressor response to noradrenaline ($P=0.032$). This effect was more marked in patients with impaired adrenal function reserve so that, as compared with patients with adequate response, the difference was no longer significant ($P=0.123$).

Conclusions In septic shock, impaired adrenal function reserve may partly be accounted for by the depressed pressor sensitivity to noradrenaline. The latter may be substantially improved by physiological doses of hydrocortisone.

Keywords: noradrenaline, dose-response curve, septic shock, adrenal function, hydrocortisone

Introduction

Septic shock is a clinical syndrome which associates sepsis with hypotension. This form of shock usually results in a dramatic fall in systemic vascular resistance and generalized blood flow maldistribution. After aggressive volume loading, the typical haemodynamic pattern consists in low vascular resistance and normal or elevated cardiac output [1]. The course of the so called 'distributive shock' may lead either to recovery or to refractory hypotension and/or to multiple organ failure, both often resulting in death [2]. If multiple organ failure probably involves complex inflammatory processes [3], the mechanism of vascular refractoriness to pressor agents remains unclear. Sepsis may induce myocardial dysfunction [4] but blood vessels contractility is also altered and this involves multiple factors [5, 6]. Firstly, enhanced nitric oxide release by the inducible form of nitric oxide synthase may account, at least partly, for by the vasodilation and resistance to vasoconstrictors [7–9]. Secondly, sepsis may be associated with a reduction in adrenoreceptor sensitivity at the level of renal [5] and skeletal [10] blood vessels. This dysfunction has also been observed at the level of myocardium [11].

Several factors including age, sodium intake, thyroid hormones and steroids have been shown to regulate both β- and α-adrenergic receptor numbers and responses [12]. Moreover, endogenous glucocorticoids maintain normal vasomotor tone of small vessels and mineralocorticoids are known to sensitize blood vessels to angiotensin and catecholamines [13]. In animals, adrenalectomy alters the number of adrenergic receptors in several tissues [14]. In human septic shock, an absolute adrenal insufficiency is rare, but an impaired adrenal function reserve (i.e. a low cortisol response to corticotrophin) is present in almost 40% of patients [15, 16]. In addition, experimental [17] and human [18–20] studies have suggested that intravenous physiologic doses of hydrocortisone may reverse the circulatory failure in septic shock.

Therefore, the purpose of our study was to assess the pressor sensitivity to noradrenaline in septic shock patients as compared with normal controls, its relationship with adrenal gland function and the effects of a physiological dose of hydrocortisone on it.

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Methods

The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Saint-Germain en Laye, France. Informed assent was obtained from the closest relative for the patients whereas informed consent was obtained from the controls.

Study population

Patients Consecutive patients admitted to the Intensive Care Unit (ICU) entered the study if they met the following criteria defining the septic shock: a) hypotension defined by a sustained (for at least 1 h) decrease in systolic blood pressure <90 mmHg, or a drop in systolic blood pressure >40 mmHg and a pulmonary capillary wedge pressure between 12 and 20 mmHg (after volume replacement) and without antihypertensive drug, myocardial infarction or evidence for pulmonary embolism, b) sepsis syndrome as previously defined [21]. Patients with autoimmune disease, immunocompromised state, receiving corticosteroids and/or any drugs that affect the cardiovascular system or the hypothalamo-pituitary axis, were not included.

Controls Nonsmoking normal subjects entered in the study to constitute the control group. Subjects were assumed to be healthy on the basis of past medical history, clinical examination, 12 lead ECG and standard biological tests. They had not to take any medication for at least 3 months.

Investigated parameters

Baseline characterization of patients with sepsis and controls The Simplified Acute Physiology Score II (SAPS II) was calculated in each patient as previously defined [22].

Systemic and pulmonary haemodynamics Systolic and diastolic systemic arterial pressures (mmHg) and heart rate (beats min^{-1}) were recorded continuously and non invasively using finger arterial blood pressure measurement (Finapress—Ohmeda 2300 NIBP Monitor, BOC Health care, Englewood, CO, USA) as validated in healthy volunteers [23] and as used in many pathological situations including impaired microcirculation [24–26]. The same method was also used for controls.

In patients, right atrial, systolic and diastolic pulmonary arterial and pulmonary capillary wedge pressures (mmHg) were measured by use of a flow-directed thermodilution pulmonary artery catheter (Baxter Healthcare Corp, Edwards Division, Santa Ana, CA, USA) introduced via the right internal jugular vein and connected to a monitor (Hewlett Packard 78353B fitted to a 78342A multichannel recorder). Cardiac output ($l\,min^{-1}$) was determined by thermodilution technique using a cardiac output computer (Baxter Healthcare Corp COM-2TM, Edwards Division, Santa Ana, CA, USA). None of these parameters was measured in controls. Finally, the following parameters were calculated by use of standard formulae: mean systemic and pulmonary arterial pressures (mmHg), and systemic and pulmonary vascular resistances (dyn s cm^{-5}).

Biological parameters Plasma l-lactate (mmol l^{-1}) was measured using routine assay. Plasma renin activity (ng l^{-1} min^{-1}), aldosterone (ng $100\,ml^{-1}$) and cyclic GMP (pmol ml^{-1}) levels were measured using radioimmunoassay [27–29]. Plasma noradrenaline (pg ml^{-1}) and adrenaline (pg ml^{-1}) levels were measured using high performance liquid chromatography [30].

Basal cortisol levels and corticotrophin stimulation test A short corticotrophin stimulation test was performed with 0.25 mg tetracosactrin (Synacthen, Ciba, Rueil-Malmaison, France) given intravenously. Blood samples were taken immediately before the test and 30 and 60 min afterwards. After centrifugation, plasma samples were stored at 4° C and cortisol (nmol l^{-1}, normal range from 165 to 785 nmol l^{-1}) was measured by enzyme linked fluorescent assay (ELFA, VIDAS Cortisol, Bio Mérieux SA, Lyon, France) within 24 h by a blinded biologist.

Assuming that, in septic shock patients, basal cortisol levels would be greater than 500 nmol l^{-1} [15, 16, 31], the cortisol response to corticotrophin stimulation was defined as the difference between the basal concentration and the highest of the 30 and 60 min concentrations and not as the peak cortisol value after corticotrophin. In these conditions, the diagnosis of impaired adrenal function reserve (AI) was established on the basis of a cortisol response less than 250 nmol l^{-1} [15, 16, 31].

Pressor response to noradrenaline The pressor sensitivity to noradrenaline was assessed by drawing the noradrenaline-mean systemic arterial pressure dose response-curve. Noradrenaline was infused stepwisely (each dose being maintained 5 min) at 0, 0.01, 0.02, 0.05, 0.07, 0.10, 0.20, 0.50, 0.75, 1.00 and 1.50 $\mu g\,kg^{-1}\,min^{-1}$. At each dose, mean systemic arterial pressure was determined as the mean value recorded within the last minute of infusion.

Study protocol

Patients Septic patients were studied at the bedside within the first 3 h of circulatory failure and before administration of any anaesthetic, inotropic or vasopressor drug and after a careful fluid replacement by infusion of hydroxyethylamidon to achieve adequate preload (i.e. a pulmonary capillary wedge pressure between 12 and 20 mmHg). All subjects successively underwent arterial blood withdrawal for biochemical and hormonal measurements, the noradrenaline infusion test and the short corticotrophin test. The noradrenaline infusion test was repeated 1 h after a 50 mg intravenous bolus of hydrocortisone. Finally, the corticotrophin stimulation test was repeated in survivors just before hospital discharge. Deceased patients underwent a careful necropsy study of the adrenal gland to assess the presence of haemorrhage and/or necrosis.

Controls At 07.00h, after a light meal, the controls arrived in the clinical investigation unit and immediately laid recumbent to normalise all parameters. An indwelling catheter with an heparinized lock was inserted into a forearm vein of the right arm and a plethysmographic cuff including an infrared detector was fitted to the middle phalanx of the

third finger, which was kept at the heart level. At 08.00 h, after a 1 h lying rest period, the basal values of heart rate, systolic and diastolic systemic arterial pressures were obtained and blood samples were taken for biochemical and hormonal measurements. Thereafter, controls successively underwent the noradrenaline infusion test and the short corticotrophin test.

Statistical analysis

Statistical analyses were performed using SYSTAT Software for Macintosh (SYSTAT: Statistics, Version 5.2. Evanston, IL, USA). In the results section, quantitative variables are expressed as means ± s.d. whereas in the figures s.e. means are used for clarity. Clinical and biological data were compared between groups (i.e. between controls and septic patients, and, within septic patients, between patients with and without impaired adrenal function reserve) using Mann-Whitney tests. In these cases, 95% confidence intervals (CI) for difference in means are also given. The pressor sensitivity to noradrenaline was compared between controls and septic patients using repeated measures ANOVA with one grouping factor (i.e. group) and one within factor (i.e. dose). The pressor sensitivity to noradrenaline was also compared between patients with and without impaired adrenal function reserve, and within septic patients before and after the hydrocortisone bolus, by two repeated measures ANOVAs, the first with one grouping factor (group: patients with impaired adrenal function reserve *vs* patients without impaired adrenal function reserve) and one within factor (dose) and the other with two within factors (treatment and dose). The pressor sensitivity to noradrenaline was compared between patients with and without impaired adrenal function reserve after the 50 mg bolus of hydrocortisone by repeated measures ANOVA with one grouping factor (group: patients with impaired adrenal function reserve *vs* patients without impaired adrenal function reserve) and one within factor (dose). Finally, the existence of a relationship between the peak adrenal response, i.e. the highest value of cortisol after corticotrophin, and the maximum increase in mean systemic arterial pressure in response to noradrenaline was investigated. Correlations between two quantitative variables were studied by computing Spearman rank order correlation matrix. For each analysis, P values ≤ 0.05 were considered statistically significant.

Results

Description of the population

Six healthy subjects (mean ± s.d., 44 ± 13 years, 69 ± 7 kg, male/female ratio = 3/3) and nine patients (51 ± 12 years, 71 ± 19 kg, male/female ratio = 6/3) were included in the study. There was no significant difference between controls and patients for both age and weight (95% CI for difference in means: [−7, 21] and [−16, 20], respectively). For patients in septic shock, the site of infection was the lung, intra-abdominal and abdomino-perineal gas gangrenous in 5, 2 and 2 cases, respectively. Gram negative bacteria were involved in four patients, *Clostridium perfringens* and *Bacteroides fragilis* in two cases and *Streptococcus pneumoniae* in three cases. Blood cultures were positive in three patients with gram negative sepsis and in the three patients with *Streptococcus pneumoniae* infection. All patients were mechanically ventilated and, at inclusion, the mean PaO_2/FiO_2 was 251 ± 120 mmHg.

Cortisol response to corticotrophin

As compared with controls, patients with septic shock had higher basal plasma cortisol levels (1564 ± 818 *vs* 378 ± 104 nmol l^{-1}, $P = 0.002$, [452, 1920]) and lower cortisol response to corticotrophin bolus (403 ± 461 *vs* 1132 ± 195 nmol l^{-1}, $P = 0.008$, [−1163, −295]) (Figure 1). The cortisol response was correlated to basal cortisol levels neither in patients with septic shock (Spearman correlation coefficient, $r = 0.34$, $P = 0.373$) nor in controls (Spearman correlation coefficient, $r = 0.65$, $P = 0.167$). In patients with septic shock, five met the criteria for impaired adrenal function reserve and four had adequate adrenal response.

Clinical and biological data in septic patients, at inclusion

As shown in Table 1, there was no significant difference between the two groups of patients for severity of illness (SAPS II), duration of shock, heart rate, and systemic and pulmonary haemodynamics (cardiac output, mean arterial pressures and vascular resistances, right and left ventricle filling pressures).

As shown in Table 2, there was no significant difference between the two groups of patients for the basal levels of cortisol, noradrenaline and adrenaline, plasma renin activity and aldosterone, and l-lactates and cyclic GMP.

Pressor response to noradrenaline

The noradrenaline test was well tolerated in all subjects. As compared with controls, in septic patients, at baseline, mean systemic arterial pressure was significantly decreased (41 ± 18 *vs* 70 ± 11 mmHg, $P = 0.006$, [−47, −11]), but the noradrenaline infusion test was associated with similar changes in heart rate (at peak effect: −35% and −37%, respectively). Moreover, in septic patients, noradrenaline did not change cardiac output (at peak effect: +1%, range −2% to +6%). As compared with controls, patients in septic shock had a slight and non significant decrease in pressor response to noradrenaline ($P = 0.112$) (Figure 2). In contrast, as compared with patients without impaired adrenal function reserve, the pressor response to noradrenaline was significantly weaker in patients with impaired adrenal function reserve ($P = 0.038$), the dose-response curve being shifted to the right and the bottom (Figure 3). The difference in response ranges, on average, from 7 mmHg (for 0.05 μg kg^{-1} min^{-1}) to 20 mmHg (for 1.5 μg kg^{-1} min^{-1}). Finally, in septic patients, the maximum increase in mean systemic arterial pressure after noradrenaline infusion was positively correlated to the peak adrenal response (Spearman correlation coefficient, $r = 0.783$, $P = 0.013$) (Figure 4).

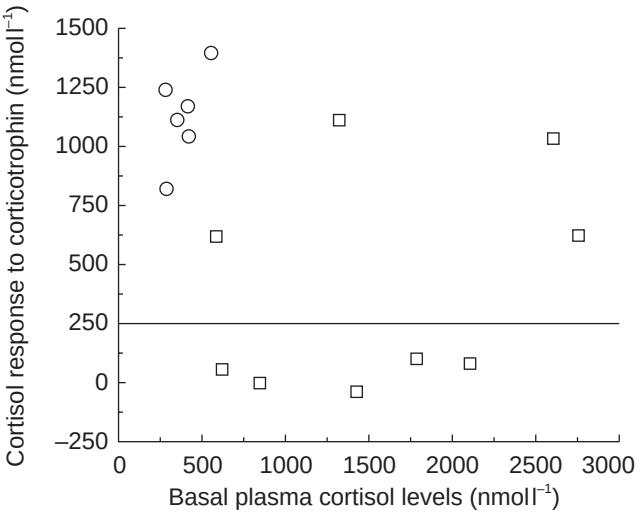

Figure 1 Patients ($n=9$; squares) and controls ($n=6$; circles) cortisol response to corticotrophin (i.e., difference between basal concentration and the highest of the 30 and 60 min concentrations after a 0.25 mg tetracosactrin intravenous bolus) as a function of individual values of basal plasma cortisol levels.

Effects of a single intravenous bolus of 50 mg hydrocortisone in patients with septic shock

In patients with septic shock, a 50 mg intravenous bolus of hydrocortisone tended to increase basal mean systemic arterial pressure (52 ± 20 *vs* 41 ± 18 mmHg, $P=0.171$, [−8, 30]). Moreover, it improved substantially the pressor response to noradrenaline ($P=0.032$), the dose-response curve being shifted to the top and the left (Figure 5). The difference in response ranges, on average, from 10 mmHg (for 0.075 $\mu g\,kg^{-1}\,min^{-1}$) to 30 mmHg (for 1.5 $\mu g\,kg^{-1}\,min^{-1}$). Finally, after hydrocortisone, the pressor response to noradrenaline was no longer different between patients with impaired adrenal function reserve and patients with adequate adrenal response ($P=0.123$) (Figure 6).

Patient's outcome

None of the patients with adequate adrenal response died. Four out of the five patients with impaired adrenal function reserve died and autopsy examination showed normal adrenal glands in three cases and haemorrhaged and necrotic glands in one patient. All survivors had normal basal cortisol concentrations and normal cortisol response to corticotrophin bolus after complete reversal of sepsis and before being discharged from the intensive care unit.

Discussion

The selected patients had severe form of septic shock as depicted by high severity score (i.e., SAPS II), high arterial l-lactate levels, and high mortality rate. As compared with controls, and as previously reported [15, 16, 31], septic patients had increased baseline cortisol concentrations, all of them being above 500 $nmol\,l^{-1}$. Thus, a peak value for serum cortisol levels below 497 $nmol\,l^{-1}$ (18 $\mu g\,dl^{-1}$) after corticotrophin, as generally proposed to define adrenal insufficiency [32], could not be used in our population to select patients without adequate adrenal function. In this population of septic shock, a weak response to corticotrophin seemed rather more appropriate [15, 16, 31]. Using this criteria, five patients had impaired adrenal function reserve. None of the patients had received exogenous steroids or had evidence of AIDS, malignancy, autoimmune disorders or any condition that may contribute to a dysfunction of the hypothalamo-hypophyso-adrenal axis [33]. Several mechanisms may be involved in the onset of impaired adrenal function reserve in septic shock and its exact pathophysiology remains unknown [16, 31]. As observed in this study, the impaired adrenal function reserve does not depend on anatomic gland lesions. The two groups being similar for severity of illness and for severity and duration of shock, it seems unlikely that impaired adrenal function reserve simply reflected widespread organ failure. The relative lack of cortisol response to corticotrophin in septic patients may be due to the fact that the normal hypothalamic-pituitary-adrenal axis was already maximally stimulated. However, it does not seem to be the case since patients with adequate adrenal function had higher basal and peak cortisol levels than patients with impaired adrenal function reserve. More probably, the blunted response to corticotrophin may be due to cytokine-mediated inhibition of corticotrophin release [32, 34].

Noradrenaline acts predominantly on α-adrenoreceptors [35]. If in theory noradrenaline may stimulate cardiac β_1-receptors, in practice and as previously reported [36], in our septic shock patients after fluid rescusitation, noradrenaline induced a strong decrease of heart rate, probably as a result of the baroreflex activation secondary to the increase in mean systemic arterial pressure. Since simultaneously noradrenaline did not significantly change cardiac output, it can be concluded that it increased stroke volume, an effect which probably results of the Frank Starling mechanism and perhaps of the stimulation of β_1-receptors. Thus, our results do not allow us to conclude there is a depressed sensitivity of β_1-receptors to noradrenaline. On the other hand, our study shows that, as compared with healthy subjects, patients with sepsis had a substantial reduction in mean systemic arterial pressure contrasting with a rather preserved pressor response to noradrenaline. *In vitro* studies with aortic rings

Table 1 Clinical data and haemodynamic parameters in septic patients, at inclusion.

Patient	*Age (years)*	*Sex*	*SAPS II*	*Duration of shock (h)*	*Heart rate (beats min^{-1})*	*Cardiac output (l min^{-1})*	*Mean systemic arterial pressure (mmHg)*	*Systemic vascular resistance (dyn s cm^{-5})*	*Mean pulmonary arterial pressure (mmHg)*	*Pulmonary vascular resistance (dyn s cm^{-5})*	*Right atrial pressure (mmHg)*	*PCWP (mmHg)*
Adequate adrenal function reserve												
1	41	M	48	2.0	102	11.2	59	493	23	192	9	20
2	61	M	53	1.0	155	11.8	37	434	20	200	7	16
3	50	F	62	2.0	105	9.0	40	450	24	184	8	13
4	45	M	73	1.0	115	8.9	55	400	20	149	4	13
Mean	49	—	59	1.5	119	10.2	48	444	22	181	7	16
s.d.	9	—	11	0.6	25	1.5	11	39	2	23	2	3
Impaired adrenal function reserve												
1	65	M	87	1.0	97	9.6	60	624	27	252	5	16
2	54	F	48	2.0	145	6.4	60	360	22	224	5	12
3	41	M	53	1.0	130	8.2	27	500	22	174	10	15
4	36	F	56	1.0	107	13.4	47	466	27	157	7	19
5	69	M	84	1.0	122	12.7	65	500	18	259	6	17
Mean	53	—	66	1.2	120	10.1	52	490	23	213	7	16
s.d.	14	—	18	0.5	19	3.0	15	94	4	46	2	3
P	.81	—	.71	.46	.90	1.00	.39	.27	.71	.39	.80	1.00
CI	[−15, 23]		[−17, 31]	[−1.2, 0.6]	[−34, 36]	[−4.0, 3.8]	[−17, 25]	[−74, 166]	[−4, 6]	[−28, 92]	[−3, 3]	[−5, 5]

SAPS II score denotes the severity of illness and PCWP = pulmonary capillary wedge pressure, M = male and F = female. Variables are given as means, standard deviations (s.d.) and 95% confidence intervals for difference in means (CI). The *P* values are those of Mann-Whitney test.

Table 2 Biochemical and hormonal parameters in septic patients, at inclusion.

Patient	*Basal cortisol* ($nmol\ l^{-1}$)	*Cortisol response* ($nmol\ l^{-1}$)	*Noradrenaline* ($pg\ ml^{-1}$)	*Adrenaline* ($pg\ ml^{-1}$)	*Plasma renin activity* ($ng\ l^{-1}\ min^{-1}$)	*Aldosterone* ($ng\ 100\ ml^{-1}$)	L-*lactate* ($mmol\ l^{-1}$)	*Cyclic GMP* ($pmol\ ml^{-1}$)
Adequate adrenal function reserve								
1	2760	635	1116	314	141	749	12.0	60
2	577	618	904	92	242	297	4.8	70
3	2622	1049	1526	212	72	362	3.2	39
4	1325	1118	439	48	100	34	5.1	29
Mean	1821	855	996	167	139	361	6.3	50
s.d.	1051	265	452	120	74	295	3.9	19
Impaired adrenal function reserve								
1	1789	99	1735	135	135	570	6.6	70
2	842	0	557	44	30	150	2.7	102
3	2109	91	237	39	37	46	2.6	20
4	621	52	698	107	111	641	3.2	100
5	1430	−39	608	92	50	467	3.9	36
Mean	1358	41	767	83	73	375	3.8	66
s.d.	625	59	568	41	47	263	1.6	37
P	.71	.02	.54	.33	.18	.90	.22	.62
CI	[−1787, 861]	[−1098, −530]	[−1056, 598]	[−218, 50]	[−161, 29]	[−426, 454]	[−7.0, 2.0]	[−33, 65]

Cyclic GMP = cyclic guanosin monophosphate. Variables are given as means, standard deviations (s.d.) and 95% confidence intervals for difference in means (CI). The *P* values are those of Mann-Whitney test.

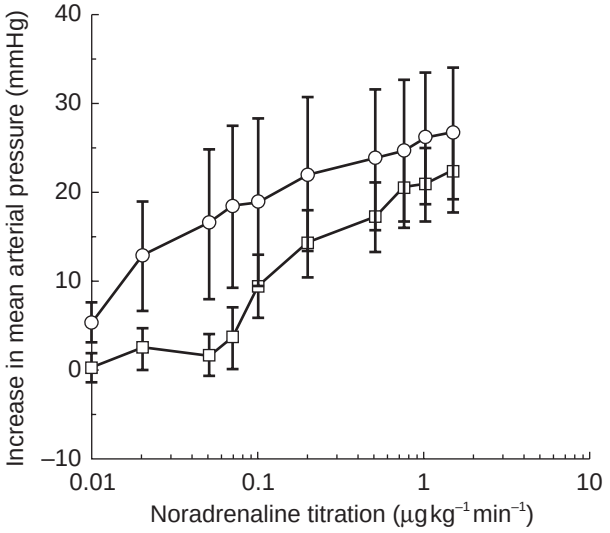

Figure 2 Increase in mean systemic arterial pressure in response to a stepwise infusion of noradrenaline in septic shock patients ($n=9$; squares) and controls ($n=6$; circles). Data are means ± s.e. mean.

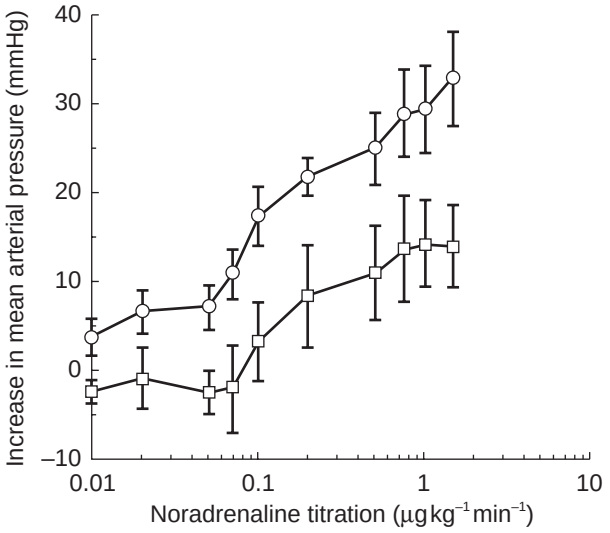

Figure 3 Increase in mean systemic arterial pressure in response to a stepwise infusion of noradrenaline in septic shock patients with impaired adrenal function reserve ($n=5$; squares) and adequate adrenal response ($n=4$; circles). Data are means ± s.e. mean.

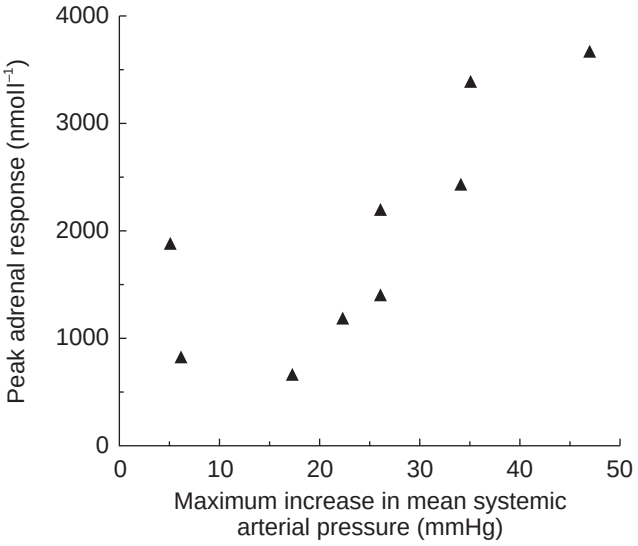

Figure 4 Maximum increase in mean systemic arterial pressure as a function of peak adrenal response after corticotrophin (i.e. highest value of plasma cortisol between 30 and 60 min after a 0.25 mg tetracosactrin intravenous bolus), in septic shock patients. Spearman correlation coefficient = 0.783 and $P=0.013$.

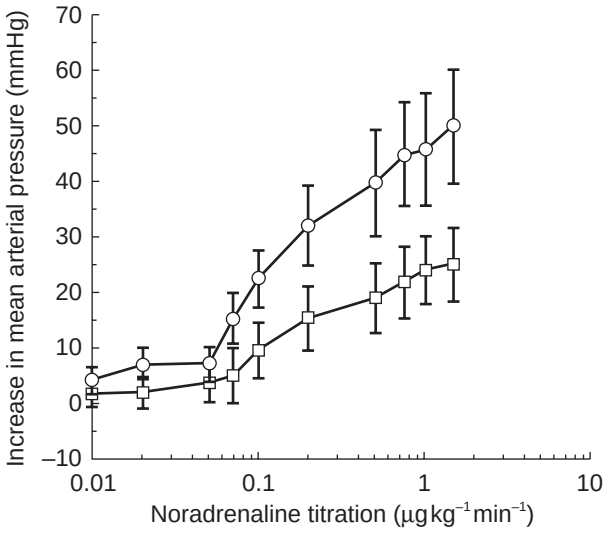

Figure 5 Increase in mean systemic arterial pressure in response to a stepwise infusion of noradrenaline in septic shock patients at baseline ($n=9$; squares) and 1 h after a 50 mg hydrocortisone intravenous bolus ($n=9$; circles). Data are means ± s.e. mean.

and isolated atria and *in vivo* studies using intact animals [37–39] suggest depressed myocardial and vascular responses to noradrenaline during sepsis. Two major points may be accounted for by the discrepancies between these experimental studies and our results. Firstly, most of the studies were performed in animals during general anaesthesia, an experimental condition which is known to alter myocardial and vascular responses to catecholamines [40]. Secondly, the above mentioned studies examined catecholamine responses immediately after an acute bolus of microbial toxins, a situation which is probably quite different from that of progressive sepsis, as seen in our patients. Indeed, one study in unanaesthetized dogs with chronic peritonitis suggests that sepsis did not affect the sensitivity of animals to noradrenaline as an α-adrenoceptor agonist [36].

Our study shows that, as compared with patients with adequate adrenal response to corticotrophin, patients with impaired adrenal function reserve had a significant decrease in pressor sensitivity to noradrenaline. Several factors may interfere with the pressor response to catecholamines, including underlying diseases that involve the heart or the circulation, previous treatments (i.e., vasodilators, steroids), preload, enhanced sympathetic activity or nitric oxide production, and lactate acidosis [12, 14]. The patients enrolled in our study had no past medical history and no previous therapy that may affect the cardiovascular system. At the onset of shock, patients with impaired adrenal function reserve and patients with adequate adrenal response to corticotrophin were comparable with regard to severity of illness, left ventricle filling pressure and cardiac output, plasma arterial l-lactate, neurohormones and cyclic GMP levels and only differed with regard to adrenal response to

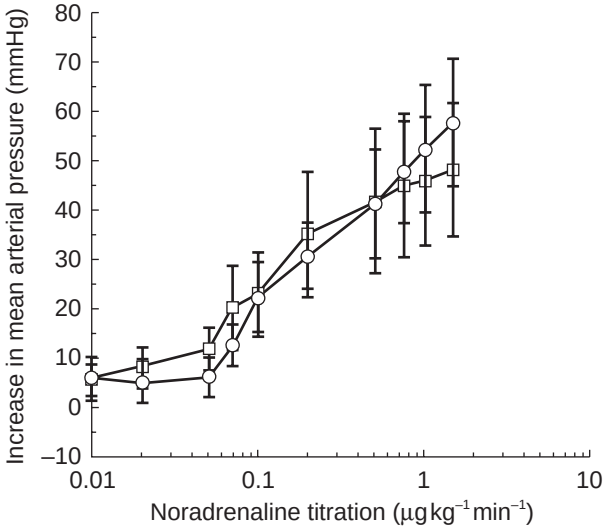

Figure 6 Increase in mean systemic arterial pressure in response to a stepwise infusion of noradrenaline 1 h after a 50 mg hydrocortisone intravenous bolus in septic shock patients with impaired adrenal function reserve ($n=5$; squares) and adequate adrenal response ($n=4$; circles). Data are means s.e. mean.

corticotrophin. Thus our results confirm that, in septic shock, an impaired adrenal function reserve may alter the pressor sensitivity to noradrenaline.

Several experimental [17] and human reports suggest that physiological [18–20] and pharmacological [41] doses of steroids may reverse the cardiovascular failure in septic shock with refractory hypotension. In our patients, hydrocortisone had only a moderate and non significant effect on baseline mean systemic arterial pressure, but it substantially improved pressor sensitivity to noradrenaline. This result is in line with those of experimental studies with the glucocorticoid antagonist RU 486 showing that glucocorticoids increase vascular reactivity to angiotensin II and noradrenaline [42, 43]. Moreover, after a 50 mg bolus of hydrocortisone, the pressor response to noradrenaline was no longer weaker in patients with impaired adrenal function reserve than in patients with adequate adrenal response to corticotrophin, thus allowing the conclusion of a more marked effect in patients with impaired adrenal function reserve. Glucocorticoids may partly reverse nitric oxide induced resistance to vasoconstrictors in septic shock [9, 44]. Indeed, in our study, cyclic GMP levels were slightly higher in patients with impaired adrenal function reserve than in those with adequate response to corticotrophin. However, other work is required to determine the possible involvement of a stimulation of the central noradrenergic system, a modification of the number and sensitivity of adrenoreceptors, an inhibition of noradrenaline reuptake or an increase in mitochondrial calcium content [42, 43].

In conclusion, our study suggests that, in septic shock after fluid replacement, the α-adrenoceptor agonist, and perhaps β-adrenoceptor agonist, effects of noradrenaline are maintained, except in cases of relative adrenal insufficiency. Physiological doses of intravenous hydrocortisone may substantially improve the pressor response to noradrenaline in septic patients, this effect being more marked in patients with relative adrenal insufficiency.

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